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ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 11/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/974,546	AN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78-84 and 86-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-84 and 86-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed April 21, 2005 is acknowledged and has been entered. Claim 85 has been canceled. Claims 78, 83, 86, 87, and 92 have been amended.

2. Claims 78-84 and 86-94 are pending in the application and are currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Grounds of Objection and Rejection Withdrawn

4. Unless specifically reiterated below, Applicant's amendment and/or arguments filed in April 21, 2005 have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed November 22, 2004.

Response to Amendment

5. In response to the amendment filed April 21, 2005 canceling claim 85, Applicant is reminded that in accordance 37 C.F.R. § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003), the text of "canceled" and "not entered" claims must not be presented.

For further explanation of the amendment format required by 37 CFR § 1.121, see MPEP § 714 and the USPTO website at:

http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf.

6. In further response to the amendment filed April 21, 2005, the amendment of the specification at page 1 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported

by the original disclosure, is: "The entire text of the above-referenced disclosure[s] is specifically incorporated by reference herein without disclaimer", insofar as the statement refers to U.S. Provisional Application Nos. 60/01,655 and 60/013,611. An incorporation-by-reference statement added after the filing date of an application is not permitted because no new matter can be added to an application after its filing date. See 35 U.S.C. § 132(a). When a benefit claim is submitted after the filing of an application, the reference to the prior application cannot include an incorporation-by-reference statement of the prior application. Therefore, the incorporation-by-reference statement in the amendment to the specification introduces new matter and renders the amendment improper. See *Dart Industries v. Banner*, 636 F.2d 684, 207 USPQ 273 (C.A.D.C. 1980). See 1268 OG 89 (18 March 2003).

Applicant is required to cancel the new matter in the reply to this Office Action.

Priority

7. Applicant's claim under 35 USC § 120 for benefit of the earlier filing date of the U.S. Patent Application No. 08/692,787, filed July 31, 1996, is acknowledged.

However, claims 78-84 and 86-94 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

Claims 78-84 and 86-94 are presently drawn to a method for treating breast or bladder cancer. While the specification of U.S. Patent Application No. 08/692,787 describes treating prostate cancer by a process comprising administering to a patient an agent that binds to and/or inhibits the activity of a polypeptide encoded by a nucleic acid molecule corresponding to the marker designated UC Band #28 (i.e., SEQ ID NO: 3), it does not describe such processes for treating breast or bladder cancer; moreover, the specification does not appear to teach or suggest the presence, or more particularly the over-expression of the gene corresponding to this marker in either breast or bladder cancer. Accordingly, the specification of U.S. Patent Application No. 08/692,787 fails to adequately describe the presently claimed invention, so as to satisfy the written

description and enablement requirements set forth under 35 U.S.C. § 112, first paragraph.

To receive benefit of the earlier filing date under 35 USC §120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of U.S. Patent Application No. 09/097,199, namely June 12, 1998.

Grounds of Objection Maintained

Specification

8. The objection to the specification because the use of improperly demarcated trademarks is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although Applicant has made a *bona fide* attempt to correct this issue in the amendment filed April 21, 2005, there are other examples of improperly demarcated trademarks (e.g., Fungizone™, which appears at page 85, line 4).

Again, appropriate corrections are required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

9. The objection to the specification because of disclosures by the impermissible referral to embedded hyperlinks and/or other forms of browser-executable code, and to the Internet contents so identified, is maintained. Reference to hyperlinks and/or other forms of browser-executable code, and thus to the Internet contents so identified, *is impermissible and therefore requires deletion.*

In replying to the preceding amendment, Applicant amended the specification to delete "http://" from the disclosure at page 119, beginning in line 8; however, the specification still contains a link, namely "www.cancer.org/statistics/98cff/98prosta.html". Even if it were the link were "inactivated", the disclosure still refers to the website, and to the Internet contents so identified.

Notably, another example of such an impermissible reference appears in the specification at page 117, line 20.

Again, the attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code, for example, (i.e., any reference to the contents of an Internet website) is considered to be an improper incorporation by reference and requires deletion.

By way of further explanation, MPEP 608.01(p) does not provide for incorporation of essential *or* non-essential material by reference to, for example, hyperlinks or other forms of browser-executable code. Essential subject matter may only be incorporated by reference to (1) US patents and pending US applications, or patents or other publications published by a foreign country or a regional patent office, (2) non-patent publications, (3) a US patent or application which itself incorporates material by reference, or (4) a foreign application. Non-essential information may be incorporated by reference to (1) patents or applications published by the United States, or patents or other publications published by a foreign country or a regional patent office, (2) prior filed, commonly owned US applications, (3) non-patent publications.

It is impermissible that a patent's disclosure incorporate essential or non-essential material by reference to, for example, embedded hyperlinks and/or other forms of browser-executable code, because the information contained in the websites or databases to which the hyperlinks or other forms of browser-executable code connect

may not be maintained on the Internet for the duration of the patent's term and may not contain the same information after the filing date of an application that was contained in the website or database on or before the filing date of the application. Since the information contained in a website may vary, it is not evident that information contained in a website will always remain useful the practitioner or even applicable to the invention; and information contained in an extinct website cannot possibly be helpful to the practitioner. Furthermore, the validity of a patent containing a reference to a hyperlink or other form of browser-executable code may be reasonably questioned if the website(s) to which the hyperlink(s) connect were relied upon by the patentee(s) to provide sufficient disclosure or description of the invention to meet the requirements of 35 USC § 112, first and second paragraphs. As such, recitation of such references is not permitted.

A hyperlink or other form of browser-executable code may be permitted if the hyperlink or other form of browser-executable code is part of the claimed invention, but in such a case, the Office would disable the hyperlink or other form of browser-executable code.

In general, if the Applicant expects to rely upon the information contained in the websites or databases referred to by such disclosures to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph, or to provide antecedent basis for the subject matter of claims in the instant application or related applications, and if the material is properly incorporated by reference in the referencing application, Applicant would be required to amend the specification of the referencing application to include the material incorporated by reference to the hyperlink or other forms of browser-executable web, or other non-permissible sources and to provide a declaration by Applicant or Applicant's representative stating that the amendatory material consists of the same material incorporated by reference in this application. See MPEP § 608.01(p).

If Applicant intends that information contained at the websites to which the disclosures refer be incorporated, Applicant is required to amend the specification to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing

Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Objections

10. The objection to claims 78-84 and 86-94 because the claims are drawn in the alternative to the subject matter of non-elected inventions is maintained. Again, appropriate correction is required.

Claim Rejections - 35 USC § 112

11. The rejection of claims 78-82, 86-91, and 94 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At pages 8-10 of the amendment filed April 21, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even

for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105).

In this instance, claims 78, 86, 87, and 94 are drawn to a method for treating cancer comprising administering a member of a genus of "agents" that bind to a peptide or polypeptide. Claims 79-82 and 88-91 are drawn to the methods of claims 78 or 87, wherein the "agent" is an antibody, as opposed to claims 83, 84, 92, and 93, which are drawn to the methods of claims 78 or 87, wherein the agent is an antibody that is conjugated or linked to a radionuclide or chemotherapeutic agent.

Ipsis verbis support for the term "agent" is found throughout the specification, including the claims, as originally filed; however, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

While the "agent" to which the claims are directed could be an immunoconjugate comprising an antibody that binds the protein and either a radionuclide or chemotherapeutic agent, the specification discloses that this genus of "agents" includes, for example, specific "inhibitors" of the polypeptide encoded by the nucleic acid sequences of SEQ ID NO: 83 or SEQ ID NO: 85. Thus, the genus of "agents" includes, for example, naked antibodies that bind the polypeptide and inhibits its specific activity or function. Moreover, while the genus of "agents" that inhibit the activity or function of the polypeptide includes such antibodies, the specification discloses the genus includes "other inhibitors" (page 18, lines 18-20), which are thereafter not described in any

additional detail. So, besides antibodies, this genus of "agents" that specifically bind to the polypeptide and inhibit its activity or function includes, for example, peptides and small molecules. Notably, such peptides and small molecules bare no apparent structural or functional relationship to antibodies that bind the polypeptide.

Thus, giving the broadest, reasonable interpretation, the claims are directed to a genus of "agents", which include naked antibodies, antibodies conjugated to radionuclides or chemotherapeutic agents, and other substances, which vary both structurally and functionally, despite their common ability to bind to the polypeptide encoded by the nucleotide sequences set forth as SEQ ID NO: 83 or SEQ ID NO: 85 and/or inhibit its function.

As explained in the preceding Office action, although the specification describes the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 as novel (page 111, Table 3), it does not disclose the specific activities or functions of the polypeptides encoded by these nucleotide sequences, which are inhibited by members of the genus of "agents" to which the claims are directed. Consequently, as further explained in the preceding Office action, the skilled artisan cannot envision such agents, which are inhibitors of an activity or function that has not been described, nor could the skilled artisan distinguish a compound capable of inhibiting the activity or function in the absence of such a description. Therefore, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Although Applicant has argued that the presently claimed invention is adequately described, the genus of "agents", which includes antibodies, is not limited to antibodies that are conjugated to radionuclides or chemotherapeutic agents, which bind the polypeptide encoded by SEQ ID NO: 83 or SEQ ID NO: 85. Instead, the genus includes structurally and functionally disparate molecules, including, for example, naked antibodies, that specifically bind to the polypeptide and inhibit its activity or function, such that treatment of cancer cells with the antibody provides therapeutic benefit.

Again, as explained previously, an antibody that binds the polypeptide may not inhibit its function, as the antibody may be agonist or otherwise, the antibody may not

affect the activity of the polypeptide. Only an antibody that binds the polypeptide, *which is conjugated to a radionuclide or chemotherapeutic agent*, could be immediately envisioned, given the otherwise inadequate disclosure of the claimed invention.

However, because a specific function or activity of the protein encoded by the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 has not been described, the skilled artisan could not envision, recognize, or distinguish an inhibitor, including an antibody, of the protein.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of antibodies that bind the polypeptide and inhibit its activity or function, so as to provide therapeutic benefit. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Notably the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, then, were the claims directed to an antibody that binds a well-characterized antigen, the written description would be met. However, the claims are not solely directed to an antibody that binds a well-characterized molecular target, but rather to a naked antibody that binds a polypeptide and inhibits its activity or function, so as to be therapeutically effective; and yet, the specification fails to describe the activity or function of the polypeptide. The specification fails to describe an antibody that binds the polypeptide to specifically inhibit its activity or function; and it fails to describe an antibody not conjugated to a radionuclide or chemotherapeutic agent, which inhibits the progression

of breast, bladder or prostate cancer. Moreover, it fails to describe the "epitope" of the polypeptide to which such an inhibitory antibody must bind.

There is factual evidence that the detailed description of an antigen, as opposed to the detailed description of an epitope of an antigen, should not always be regarded as sufficient to describe the antibody that binds that antigen, particularly in instances where binding of the antibody modulates the activity of the antigen. For example, Stancoviski et al. *(Proceedings of the National Academy of Science USA.* 1991; **88**: 8691-8695) characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1). By way of explanation, Jiang et al. (*J. Biol. Chem.* 2005 Feb 11; **280** (6): 4656-4662) teaches that it is well known that different biological effects are associated with epitope specificity of the antibodies; see entire document, particularly page 4656, column 2.

Accordingly, the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well-characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish those antibodies that bind an antigen on tumor cells and inhibit the growth of those tumor cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of tumor cells).

Furthermore, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to specifically bind a polypeptide and inhibit its activity, or the ability to bind a cancer cell and inhibit its growth or metastatic progression, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a

representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without the "agents" (e.g., naked antibodies that bind the polypeptide and inhibit its activity, so as to be therapeutically effective) to which the claims are directed, it is impossible to use the claimed invention.

In addition, although the skilled artisan could potentially screen candidate agents (e.g., antibodies) to identify those that bind the polypeptide and inhibit its function, so as to be therapeutically effective in treating breast, bladder or prostate cancer, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Thus, while Applicant's arguments traversing this ground of rejection have been carefully considered, they have not been found persuasive, as the disclosure fails to satisfy the "written description" requirement set forth under 35 U.S.C. § 112, first paragraph.

12. The rejection of claims 78-84 and 86-94 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At pages 10-13 of the amendment filed April 21, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth

of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Careful consideration of these factors indicates that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the "written description" rejection above, the claims are drawn to a method for treating cancer comprising administering a member of a genus of "agents" that bind to a peptide or polypeptide, so as to be therapeutically effective. While the "agent" could be an antibody that binds the protein and which is conjugated to a radionuclide or chemotherapeutic agent, the specification discloses that this genus of "agents" includes "inhibitors" of the polypeptide encoded by the nucleotide sequence of SEQ ID NO: 83 or SEQ ID NO: 85. As explained in the preceding Office action, although the specification describes SEQ ID NO: 83 and SEQ ID NO: 85 as novel (page 111, Table 3), it does not teach the specific activity or function of the polypeptide encoded by these nucleic acid sequences. Because the function or activity of the polypeptide is not disclosed, the skilled artisan could not use the claimed invention without first having to perform undue and unreasonable additional experimentation to first determine the function or activity of the protein, secondly to determine whether the function or activity of the protein correlates with the onset or progression of cancer, and if so, then to design or discover a compound that inhibits that function or activity, which can be used in practicing the claimed invention to treat breast, bladder or prostate cancer.

Although the specification asserts it is possible to predict protein function, in some cases, from primary sequence data, provided that sequence homology exists between the unknown protein and a protein of similar sequence and known function, in this instance, the specification does not disclose whether the polypeptide encoded by SEQ ID NO: 83 or SEQ ID NO: 85 bear any significant and substantial homology to other proteins of known functions and activities. Moreover, as evidenced by Skolnick et

al. (of record), for example, the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate. Thus, contrary to the assertions set forth in the instant disclosure, the skilled artisan cannot reliably and accurately predict the function of a novel protein upon the basis of only an observed similarity in its amino acid sequence and those of other proteins having known functions.

In fact, the specification, itself, supports this very position, since it discloses, "Inhibitors could also potentially be designed for the previously unreported prostate, bladder or breast cancer-markers identified in the present invention [but this] is complicated by the fact that no specific function has been identified for most of these gene products, and no data is available on their three-dimensional structures" (page 71, lines 1-6).

It was further noted in the preceding Office action that even if the function or activity of the polypeptide were known, the skilled artisan could still not use the claimed invention without first having to perform undue and unreasonable experimentation, because the specification does not teach the skilled artisan to make an inhibitor of the polypeptide, which, in particular, can be used in practicing the claimed invention to treat cancer. Additionally, even though cancer cells may overexpress the protein, its function or activity may not be associated with the onset or progression of cancer; therefore, an inhibitor of the polypeptide may not inhibit the onset or progression of cancer in the patient and would therefore not provide an effective treatment of cancer. Consequently, before designing or striving to discover an inhibitor of the protein, the skilled artisan would have to determine if such an inhibitor might be therapeutically valuable.

Inasmuch as the claims are directed to antibodies, as explained in "written description" rejection above, not all antibodies are reasonably expected to be capable of inhibiting the activity and function of the polypeptide. Other antibodies may not have any effect upon its activity or function, whereas some antibodies may actually act as agonists, promoting or enhancing its activity or function, rather than inhibiting the polypeptide.

Claims 83 and 92 are directed to antibodies that bind the polypeptide, which are conjugated to a radionuclide. In general, an antibody that binds selectively to a cancer cell, which is conjugated to a radionuclide, may be used to treat the disease, since it provides exposure to the radioactivity, which is toxic to the cells. However, as explained in the preceding Office action, while the specification teaches the protein has been localized to epithelial cells, "mainly on the cell membrane" (page 117, lines 10-14), the specification does not actually teach whether the protein is expressed at the surface of the cells. If the inhibitor is an antibody or another type of inhibitor that binds directly to the polypeptide, and the polypeptide is not expressed at the surface of the targeted cancer cells, the antibody or other inhibitor cannot specifically bind those cells and therefore will have no specific inhibitory effect upon those cells. As further noted in the preceding Office action, it is believed that An et al. (of record) provides factual evidence that the protein, which is designated therein as UROC28, is not expressed at the surface of cells. An et al. teaches immunohistochemical analyses of glandular epithelial cells of prostate and breast cancers revealed the protein localizes in the nucleus and cytoplasm; see entire document, particularly page 7018, Figure 5.

Applicant has provided a copy of a declaration under 37 C.F.R. § 1.132 by Dr. Veltri, which was filed during prosecution of a copending, related application (i.e., U.S. Patent Application No. 09/966,762). Applicant has argued that this declaration provides factual evidence that the polypeptide (i.e., UROC28), or at least a portion thereof, is present at the extracellular surface of prostate cancer cells.

The merit of the declaration filed in the copending application has been carefully considered to the extent that it is believed to be applicable to the issues raised herein.

Dr. Veltri has suggested that An et al. does not teach the protein was *not* expressed as an extracellular, plasma membrane-associated, or trans-membrane protein, only that it was *primarily* localized in the cytoplasm (i.e., the inside of the cell) and more particularly, to at least some extent, in the nucleus; see item #7 at page 3. Agreeably, An et al. does not teach that the protein, or a portion thereof, was *not* exposed at the cell's extracellular surface; but, if it was, its presence or level of expression at the extracellular surface must not have been remarkable.

The declaration states, "the present specification discloses [...] a significant of UC28 localizes to the cell membrane" (item #9 at page 3). There is, however, no factual evidence attached to the declaration to support this assertion. As explained in the preceding Office action, while the instant specification teaches the protein has been localized to epithelial cells, "mainly on the cell membrane" (page 117, lines 10-14), the specification does not actually teach whether the protein is expressed at the surface of the cells. Given the methodology and resolution of the microscopy used by An et al. it is submitted that it would not be possible to reasonably conclude that the protein is exposed at the surface of the cell; if such, methodology was used by Applicant to determine that the protein is "mainly on the cell membrane", it is further submitted that, using such methodology, one could not reliably distinguish a protein that is localized on the inside surface of the plasma membrane from a protein that is localized in the cytoplasm, or a protein that is transmembrane protein. Because the tissue sections used in the process are fixed and permeabilized, the antibody is capable of binding antigens both inside and out. Furthermore, the antibody that was used was a polyclonal antibody, so it recognizes many different antigenic determinants on the protein, not just antigenic determinants present on a putative extracellular domain; therefore, at the resolution used, it would not be possible to determine with any degree of certainty whether the protein is exposed at the surface of living cells.

The specification the protein has been localized to epithelial cells, "mainly on the cell membrane" (page 117, lines 10-14), but as evidenced by Maddala et al. (*Exp. Cell Res.* 2005; **306**: 203-215), for example, not all proteins that appear localized "mainly on the cell membrane" are transmembrane proteins comprising an extracellular domain that is accessible to an antibody at the outside surface of the cell; see entire document (e.g., the abstract). Maddala et al. teaches localization of α-crystallin, an intracellular protein, to the leading edges of the plasma membrane of lens epithelial cells; see, e.g., the abstract. This protein associates with the plasma membrane, but it is not a transmembrane protein. Using the methodology exemplified by An et al., how might one distinguish a protein, such as α-crystallin from a transmembrane protein, given that

both proteins would appear to localize to the plasma membrane? At the resolution used by An et al., it is submitted that such a distinction could not be made with reasonable certainty. The specification provides no factual evidence that suggests that the protein encoded by nucleotide sequences SEQ ID NO: 83 or SEQ ID NO: 85 is a transmembrane protein, as opposed to an intracellular protein that associates with the plasma membrane. The declaration asserts that the protein is accessible to an antibody at the surface of prostate, bladder and breast cancer cells, but provides no factual evidence to support the assertion. An et al., on the other hand, suggests the protein is not a transmembrane protein, but instead a soluble protein localized primarily to the cytoplasm and nucleus.

The declaration further states the use of conventional confocal fluorescence microscopy limited the ability of An et al. to more specifically characterize the localization of the protein and suggests the specification teaches the use of other methodology that remedies the inadequacy of their earlier methodolgy, so as to have permitted the accurate localization of the protein to outside surface of the plasma membrane. Agreeably, the methodology used by An et al. would not permit one to accurately localize the protein, or a portion thereof, to the outside surface of the cell. As evidenced by, for example, the attached references (i.e., Takizawa et al. (*J. Nippon Med. Sch.* 2004; **71** (5): 306-307) and Maddala et al. (*supra*)), the resolution of the microscopy used by An et al. would not have permitted such a conclusion. However, contrary to the statement by Dr. Veltri, there does not appear to be any disclosure in the instant specification of the use of high-resolution confocal immunofluorescent microscopy to localize the protein. In fact, the words "confocal" and "microscopy" do not appear in the specification. Thus, if any merit of the declaration is extended to the instant application, it is not known to which disclosures in the instant specification Dr. Veltri would have referred as providing remedy to the inadequacy of the methodology used by An et al.

The declaration notes the presence of a *putative* transmembrane domain in the protein and states, "the presence of this putative transmembrane domain indicates that UC28 localized to the cell membrane" (item #6). If the domain is only a *putative*

transmembrane domain, it has not yet been determined to *be* a transmembrane domain. The disclosure by An et al. suggests that the protein is not present at the extracellular surface, as if it were, its presence there was unremarkable. An et al. teaches the protein primarily localized to the inside of the cell (i.e., the cytoplasm and the nucleus); the results disclosed by An et al. do not suggest that the protein comprises an extracellular domain, or that at least part of the protein is exposed at the surface of cancer cells.

Applicant has referred to Carrol (Exhibit A); Carrol has written a commentary addressing the importance of findings disclosed by Milowsky et al. that an antibody that specifically binds protate-specific membrane antigen (PMSA), which is radiolabeled, can be used to treat patients with prostate cancer. Notably, Carrol comments that the antigen to which the antibody binds is an excellent target because it is not secreted like PSA or PAP. As mentioned in the preceding Office action, An et al. suggests that the polypeptide encoded by SEQ ID NO: 83 or SEQ ID NO: 85 (i.e., UROC28) is secreted, as it was detected in serum specimens acquired from patients diagnosed with prostate cancer (see, e.g., page 7018, figure 6). Accordingly, Carrol provides factual evidence that the polypeptide is a less desirable target than PMSA since it is secreted. Furthermore, Carrol emphasizes that the reason that PMSA is an excellent target is that the antibody that recognizes it binds tightly to its extracellular domain, as previous monoclonal antibodies bound to an intracellular domain only accessible in already dead or dying cells. Here, as explained above, it is not known whether the protein comprises an extracellular domain that might serve as the target of an antibody, which is conjugated to a radionuclide. To any extent that Carrol might provide support for Applicant's assertion that the claimed invention can be used without undue and/or unreasonable experimentation, that evidence is merely anecdotal. Again, the antibody or other inhibitor to which the claims are directed cannot effectively bind the protein, if it is present only *within* living cancer cells, and if the protein is secreted, while the antibody or inhibitor could bind the protein, it's binding to the protein will not affect the cancer cells that secreted the protein.

Claims 84 and 93 are directed to antibodies that bind the polypeptide encoded by the nucleotide sequence of SEQ ID NO: 83 or SEQ ID NO: 85, which are linked to chemotherapeutic agents. As evidenced by Vitetta et al. (of record), for example, there are well known limitations in the art of antibody-targeted therapeutic regimens; but, as explained in the preceding Office action, if a cancer cell does not express the protein that is specifically bound by the antibody at its surface, the use of a pharmaceutical composition comprising such an antibody will not be effective. The specification provides no guidance as to which chemotherapeutic agents are linked to the antibody, so as to provide the claimed therapeutic effect, but it is aptly noted that many chemotherapeutic agents, unlike radionuclides, must gain access to the inside of the cell to cause harm to the cell. Generally, an immunoconjugate comprising such a chemotherapeutic agent binds an antigen at the surface of the cell, which is then "internalized" by the cell; however, not all antigens (e.g., receptors) are "internalized" and thus many antigens to not constitute suitable targets for such therapeutic agents. Not only is it not known that the protein encoded by the nucleotide sequence of SEQ ID NO: 83 or SEQ ID NO: 85 comprises a suitable extracellular domain, but it is also not known whether the protein is "internalized" by the cell following the binding of an antibody.

Furthermore, as Bodey et al. (of record) teaches, the use of such a pharmaceutical composition may paradoxically serve to select against tumor cells that express the protein, while promoting the growth of tumor cells that do not express the protein. It is here again noted that the specification does not teach the activity or function of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 83 or SEQ ID NO: 85; and moreover, although the gene encoding the polypeptide is over-expressed, it is not known whether the polypeptide plays an essential role in the life of the cancer cell, but if it does not, it follows that the use of the claimed invention may lead only to selection against tumor cells that do not express the polypeptide.

Consequently, even if the activity of the protein were known to be essential to the life of the cancer cell, as evidenced by Gura (of record), for example, the art of anticancer drug discovery is unfortunately hindered by the extreme complexity of the

biological system and its inherently unpredictable nature. Consequently an inhibitor of the polypeptide (i.e., a naked antibody or "other inhibitor" of the polypeptide) cannot be recognized or made by routine experimentation alone.

It is further noted that the specification does not actually teach that the polypeptide of SEQ ID NO: 84 and SEQ ID NO: 86, which is expressed by the polynucleotides of SEQ ID NO: 83 or SEQ ID NO: 85, is over-expressed in cancer cells, compared to normal cells of the same tissue type. Moreover, the specification fails to demonstrate a correlation between the level of mRNA expression and the level of protein expression in cancer cells.

In response, Applicant has argued that An et al. teaches the protein is overexpressed in prostate and breast cancer cells. Indeed, using immunohistochemistry to analyze the expression of the protein in formalin-fixed paraffin sections of prostate and breast tumor specimens, An et al. discloses the level of the protein is increased in the prostate cancer glandular epithelial cells and breast cancer ductal epithelial cells as compared to the corresponding normal cells; see, e.g., page 7017, the paragraph bridging columns 1 and 2. However, Applicant is reminded that supporting documents published after the filing date sought by Applicant cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See MPEP § 2164.05(a).

Furthermore, despite teaching its overexpression in breast and prostate cancer cells, An et al. does not teach whether the protein is overexpressed in bladder cancer cells. Again, as evidenced by Chen et al. (of record), for example, one cannot presume that the amount of protein produced in a cell will mirror the amount of mRNA produced. As explained previously, this fact is so universally accepted, it is mentioned in a textbook (i.e., Genes VI, 1997) (of record).

As explained in the preceding Office action, if the protein is expressed at the surface of cells, and the inhibitor is an antibody, unless the cancer cells, relative to normal cells of the same tissue type, more abundantly express the protein, the antibody will not selectively target cancer cells, but will also undesirably target normal cells. One

skilled in the art could therefore not use the claimed invention without first performing an undue amount of additional experimentation to determine if the protein encoded by the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 is over-expressed in bladder cancer cells, compared to normal cells of the same tissue type.

In conclusion, although Applicant's arguments traversing this ground of rejection have been carefully considered, upon equally careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there is a preponderance of factual evidence of record indicating that the amount of guidance, direction, and exemplification disclosed in the specification would be insufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

13. The rejection of claims 78-82, 86-91, and 94 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

It does not appear that Applicant has traversed this ground of rejection.

Reiterating the ground of rejection as it applies to the present claims, claims 78-82, 86-91, and 94 are indefinite because claims 78 and 87 recite the phrase "effective amount". The phrase "effective amount" is indefinite when the claims fail to state the function that is to be achieved. See *In re Frederiksen & Nielsen*, 213 F 2d 547, 102 USPQ 35 (CCPA 1954). The specification discloses the agents to which the claims are directed (i.e., agents that are not conjugated or linked to radionuclides or chemotherapeutic agents) inhibit the activity of the polypeptide, so as to provide therapeutic effect. However, in this instance, it cannot be determined if the claim requires the "effective amount" of said agent to be sufficient to effectively inhibit the polypeptide, or to effectively treat cancer in the patient, or both. Notably, it is entirely possible that an amount of an agent can effectively inhibit an activity of protein, but be insufficient to inhibit the growth of tumor cells. Therefore, the claims would not reasonably apprise the skilled artisan of the metes and bounds of the subject matter

that Applicant regards as the invention, so as to permit the skilled artisan to determine infringing subject matter.

Double Patenting

14. The provisional rejection of claims 78-84 and 86-94 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-38 and 65-72 of copending Application No. 09/966,762, is maintained.

At pages 13 and 14 of the amendment filed April 21, 2005 Applicant has stated that if required, a terminal disclaimer will be filed upon an indication of allowable subject matter.

Applicant's statement is noted but until a terminal disclaimer is filed, or rendered moot by other means, this ground of rejection will be maintained.

Reiterating the ground of rejection as it applies to the present claims, although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims are drawn to a method for treating breast, bladder or prostate cancer cells comprising administering an "agent" (e.g., inhibitor), or more particularly an antibody that binds to a peptide or polypeptide encoded by SEQ ID NO: 83 or SEQ ID NO: 85, which the instant specification discloses is a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 84 and SEQ ID NO: 86.

Claims 1-38 and 65-72 of the copending application are drawn to a method for inhibiting cancer cells in a patient comprising administering to the patient a "UC28 inhibitor", including a polyclonal or monoclonal antibody that binds "UC28".

SEQ ID NO: 84 of the instant application is identical to SEQ ID NO: 2 of the copending application. The protein comprising this amino acid sequence is designated "UC28" by both the instant and copending applications; see, e.g., page 12, lines 24-27 of the copending application; and page 19, line 4, and page 115, lines 11-15 of the instant application.

The claims of the copending application do not explicitly recite that the antibody administered is conjugated or linked to a radionuclide or chemotherapeutic agent;

however, the claims of the copending application do explicitly recite that the antibody can be conjugated to a "toxin", which is defined as either a chemotherapeutic agent or a radionuclide (page 89, lines 2 and 3).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

New Grounds of Objection

Specification

15. The specification is objected to because at page 2, beginning in line 8, it states that the application is a continuation of U.S. Patent Application Serial No. 09/662,270; however, according to the transmittal letter filed October 10, 2001, this application is a divisional application, filed under Rule 53(b) (37 C.F.R. § 1.53(b)), of the co-pending application. Appropriate correction is required.

Conclusion

16. No claim is allowed.

17. The art made of record cannot be relied upon but is nonetheless considered pertinent to applicant's disclosure. WO 98/04689 A1 teaches a treating prostate cancer by administering to a patient an antibody that binds to a polypeptide encoded by a gene corresponding to the human prostate cancer marker UC Band #28 (i.e., SEQ ID NO: 3); see, e.g., page 41, lines 10-17; page 50, lines 1-7; page 113, lines 25-27; and claims 53 and 62.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
November 4, 2005